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Duration of untreated psychosis: A proposition regarding treatment definition.

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Duration of untreated psychosis: A proposition regarding treatment definition.

THESE

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par

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Duration of untreated psychosis: a proposition regarding treatment definition

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“Duration of untreated psychosis:

A proposition regarding treatment definition.”

Rapport de synthèse

La durée de psychose non traitée (Duration of Untreated Psychosis, DUP) est définie par le temps écoulé entre l’émergence d’un trouble psychotique et le début de son traitement.

La réduction de la DUP est un des objectifs principaux des programmes spécialisés dans le traitement de la psychose émergente, de nombreux travaux de recherche suggérant qu’une DUP longue est associée à une évolution défavorable de la maladie. Ces résultats restent cependant controversés, certaines études ne démontrant pas une telle association. Cette contradiction dans les résultats pourrait être la conséquence d’un manque d’uniformité dans les définitions appliquées pour mesurer la DUP, plus particulièrement en ce qui concerne la définition de ce que l’on considère être « début » du traitement. En effet, si l’étude de la phase d’émergence de la pathologie psychotique a été le focus d’une attention considérable qui a conduit à un certain degré de consensus quant à sa définition, le concept de début du traitement n’est clairement pas défini de manière aussi homogène. Compte tenu de l’importance des enjeux relatifs à l’intervention précoce dans les troubles psychotiques, il nous a semblé utile d’explorer cette question de manière plus approfondie, considérant qu’un manque de consensus dans la définition de la DUP contribue certainement à troubler les résultats des études qui visent à évaluer son impact sur l’évolution de ces maladies. En conséquence, l’objectif premier de ce travail est d’explorer l’impact de l’application de diverses définitions de début de traitement sur l’estimation de la DUP.

Dans un premier article, publié dans Acta Neuropsychiatrica en 2009 (*Duration of untreated psychosis : What are we talking about ?*), le focus a été placé sur une revue de littérature concernant les définitions utilisées pour caractériser la fin de la DUP ainsi que sur les conséquences possibles d’un manque de précision dans cette définition sur l’évaluation de l’impact d’un retard de traitement dans la psychose débutante. Ce travail nous a permis d’identifier trois groupes principaux de définition de fin de DUP (End of DUP ; E-DUP) parmi les multiples critères utilisés dans les études publiées. E-DUP-1 est définie par la mise en route d’un traitement antipsychotique, le plus souvent sans tenir compte ni du dosage prescrit, ni de l’adhérence au traitement. E-DUP-2 est définie par l’entrée dans un programme de traitement spécialisé, et E-DUP-3 enfin est définie par la conjonction de la prescription d’un traitement antipsychotique adapté, de l’adhérence à ce traitement, et de la mise en route d’une prise en charge dans un programme spécialisé. En conclusion, nous relevions que cette grande variété dans les définitions appliquées pour l’évaluation de la DUP avait probablement contribué à l’aspect contradictoire des résultats des études de son impact sur l’évolution des psychoses et qu’il était donc temps de proposer une définition de consensus.

La deuxième étude a été conduite dans le cadre d’un suivi de cohorte mis en place dans le programme de Traitement et Intervention Précoce dans les troubles Psychotiques (TIPP) établi dans le Département de Psychiatrie du CHUV à Lausanne depuis 2004. Les objectifs de cette seconde étude étaient au nombre de trois: (1) Exploration des variations de la DUP en fonction de l’application de trois principales définitions de fin de DUP (E-DUP) identifiées dans la littérature ; (2) Evaluation de la proportion de patients remplissant au moins une fois au cours des 18 mois de traitement la définition de E-DUP la plus compatible avec les directives de traitement proposées par l’International Early Psychosis Association (patient est à la fois engagé dans le traitement et se montre compliant à la médication, E-DUP-3); (3) Enfin, identification des

facteurs qui caractérisent les patients qui ne remplissent jamais les critères de cette dernière définition.

L'exploration de différentes durées de DUP en utilisant les trois définitions d'E-DUP a donné les résultats suivants : La DUP1 médiane (2.2 mois) était significativement plus courte que la DUP2 (7.4 mois), et la DUP3 (13.6 mois) était significativement la plus longue des trois.

De plus, 19.7% des patients n'avaient jamais rempli les critères de E-DUP-3 ; on peut donc considérer que près de 20% des patients traités dans ce programme spécialisé ne recevaient pas un traitement adéquat selon les directives intrernationales actuellement reconnues. Sur la base de ces chiffres, il apparaît clairement que, dans les études de l'impact de la DUP sur l'évolution de la psychose débutante, bon nombre des patients pour lesquels on considère que la DUP est terminée ne sont en fait pas adéquatement traités. Il est en conséquence très probable que ceci ait faussé les résultats de ces études, et qu'une définition plus restrictive permettrait de répondre de manière plus précise à cette question.

Les patients qui ne remplissaient pas les critères E-DUP3 au cours des 18 premiers mois de traitement étaient caractérisés par un moins bon niveau de fonctionnement au cours de leur vie (« lower lifetime SOFAS » ; $p=0.017$) et ils étaient plus susceptibles de consommer du cannabis à l'entrée du programme TIPP ($\chi 2$ (1, n=49)=4.241, $p=0.039$).

Pour ceux qui avaient rempli les critères E-DUP-3 au cours des 18 mois, une longue DUP3 était associée avec un jeune âge au début des symptômes psychotiques ($rs =-0.573$, $p<0.001$), et avec un faible niveau de fonctionnement pré-morbide (score de PAS élevés ($rs =0.373$, $p=0.001$), niveau maximal au cours de la vie bas pour le GAF($rs =-0.367$, $p<0.001$) et pour le SOFAS ($rs =-0.314$, $p=0.003$)).

En conclusion, ce travail a permis de mettre en évidence une grande variabilité dans la définition de la fin de la DUP parmi les études publiées jusque à ce jour, et l'impact important que le choix d'une ou l'autre de ces définitions peut avoir sur l'estimation de la DUP. De plus, nous avons observé que malgré la mise en place d'un programme spécialisé, près de 20% des patients ne remplissent pas les critères d'exposition à un traitement adéquat au cours des 18 premiers mois de prise en charge. Il est donc probable que l'estimation de l'impact de la DUP ait été faussé par cette variabilité, et il semble important que la communauté scientifique s'accorde sur une définition plus rigoureuse de cette variable. Enfin, certaines caractéristiques permettent d'identifier les patients qui sont à risque de ne pas remplir les critères de traitement adéquat a cours des 18 premiers mois de prise en charge ; il est possible qu'une identification précoce de ceux-ci permette la mise en place de stratégies mieux adaptées pour les aider à s'engager dans les soins.

Le futur développement de ce travail sera d'évaluer l'impact de la DUP sur l'évolution des patients au cours des 36 mois de traitement proposés dans le programme TIPP, en appliquant les divers critères E-DUP, afin de voir si notre hypothèse que la variation des définitions a effectivement faussé les résultats de telles études. Nous devons pour cela attendre qu'un nombre suffisant de patients ait complété les 36 mois de traitement, de manière à avoir une puissance statistique suffisante pour répondre clairement à cette question.

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ACTA NEUROPSYCHIATRICA

Editorial

Duration of untreated psychosis: What are we talking about?

Duration of untreated psychosis (DUP) broadly refers to the time elapsing between onset of psychosis and treatment initiation. Its relationship with outcome has been intensely studied in the framework of the development of early intervention strategies for psychosis. Results of such research are however still a matter of controversy, some studies showing a negative impact of long DUP on outcome (1–4) while others do not (5–8). In a systematic literature review, Marshall (9) nevertheless concluded that there is a significant, albeit small to moderate, negative association between DUP and outcome, and most early intervention programmes rank reduction of DUP as a primary priority.

From a clinical point of view, reduction of DUP emerges as a logical target when witnessing the collateral damage suffered by patients who experience long delays prior to onset of care (10). Additionally, recent imaging data have shown that the prodrome and the early phase of psychotic disorders are periods of active and progressive structural changes in key brain areas such as the hippocampus (11). If one assumes that there is an active process of neuroprogression underlying these changes, then the longer the DUP, the greater the time available for this potentially neurotoxic process to unfold (12). The nature of the pathogenic process remains to be fully elucidated; however, it probably includes reduction in neurotrophins, oxidative stress and inflammatory cytokines. Given the evidence that appropriate treatment is potentially neuroprotective (13), reduction in DUP could therefore be associated with reduction in potentially cumulative brain insult, and hence improvement in symptomatic and functional outcomes.

In the last few years, assessment of psychosis onset has been the object of a considerable attention, and this interest has led to both a degree of consensus about its definition and the development of scales specifically designed to determine the date of its initial occurrence (14,15). A closer look at this literature reveals on the other hand that criteria applied to define the endpoint of DUP, in other words the time of treatment initiation, is much less consistent and vary greatly between studies.

According to international guidelines, an adequate treatment of first episode psychosis should combine adapted medication (generally utilising low-dose strategy) and psychosocial intervention delivered in the context of easily accessible and specialised treatment teams (16–18). However, despite the availability of such guidelines, the concept of 'treatment initiation' usually refers to the commencement of very incomplete and often ill-defined interventions (Table 1). These include 'initiation of medication', 'commencement of any form of treatment', 'initiation of adequate treatment', 'time of first effective treatment', as well as 'hospitalisation' or 'entry to a specialised programme'. In addition, adherence to treatment is in the vast majority of cases not assessed when in fact clinical experience reveals that enrollment in a specialised service or prescription of medication does not necessarily equate with the person being fully engaged with the service, receiving sufficient psychosocial support, or taking medication as prescribed.

In the studies mentioned above, it is therefore highly likely that many patients for whom DUP was defined as having concluded actually remained untreated or partially treated. Only two studies defined treatment initiation on the basis of adherence to or observed response to medication treatment (14,30). However, by focusing on this aspect of treatment, they neglect the importance of psychosocial intervention in the recovery process (31), while recent randomised controlled trials have now clearly proven that integrated early intervention programmes that include specialised psychosocial treatment lead first episode psychosis patients to a better outcome than generic mental health programmes (32,33).

This lack of consistency in definition is concerning, considering that an absence of consensus on what 'treatment initiation' actually comprises could very well be one of the critical factors that so far

Table 1. Definitions of treatment initiation in the literature

Study	Definition applied to initiation of treatment	Limitations
Barnes et al. (19); Browne et al. (20); Craig et al. (5); Haas et al. (21); Ho and Andreasen, (7); Szymanski et al. (22); Tirupati et al. (23).	Initiation of medication	• Absence of assessment of adherence to treatment • Does not take into account psychological and case management intervention
Wiersma et al. (24)	Any form of treatment	• Absence of definition of treatment
Larsen et al. (25)	Initiation of adequate treatment	• Absence of definition of response
Addington et al. (26)	First effective treatment	• No definition of effective treatment • Problem with treatment resistance
Hafner et al. (27); Kalla et al. (28)	Hospitalisation	• Selection bias towards patients with more acute symptoms
Carbone et al. (29); Schimmelmann et al. (4)	Entry to specialised programme	• Does not mean patients are adherent to treatment
Malla et al. (30)	Medication for at least 2 months or significant response	• Treatment definition restricted to medication
Singh et al. (14)	Medication with adherence (at least 75% of the dose for 75% of the time)	• Treatment definition restricted to medication

limited the conclusiveness of studies exploring potential consequences of DUP. While research exploring DUP impact on outcome should not interfere with common sense arguments justifying the necessity of mental health services reforms aimed at facilitating treatment access for patients with psychosis (10), conclusive research on DUP, based on valid data, would only provide more momentum to such a reform process.

It seems therefore timely to establish a clearer definition of what should be considered as the end of the DUP period. First, given that medication is a key element in treatment of the vast majority of first episode psychosis patients, antipsychotic treatment initiation should belong to the definition. However, adherence to treatment ought to be assessed as well and the medication criterion considered fulfilled only if patients have taken their treatment for at least 75% of the time during at least 4 weeks. Second, based on the above data supporting the efficacy of specialised treatment, end of DUP should be considered only when patients are well engaged in an early intervention programme. It is clear that psychosocial treatments remain inconsistently available, and subject to the vagaries of service, economic, training and resource variables, but this is precisely what research on the impact of DUP is all about: to show that adequate treatment provided early has a positive impact on outcome of psychosis. Once this point established, the argument to justify the need for a reform of mental health programmes and for an earlier access to adequate psychosocial and medication treatment in early psychosis would only be stronger. However, in order to supply evidence-based arguments to this debate, the definition of DUP needs to be applied with more precision.

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Title: Duration of untreated psychosis: a proposition regarding treatment definition.

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Abstract

Aim: Duration of untreated psychosis (DUP) refers to the time elapsing between psychosis onset and treatment initiation. Despite a certain degree of consensus regarding the definition of psychosis onset, the definition of treatment commencement varies greatly between studies and DUP may be underestimated due to lack of agreement. In the present study three sets of criteria to define the end of the untreated period were applied in a first-episode psychosis cohort to assess the impact of the choice of definition on DUP estimation.

Method: The DUP of 117 patients admitted in the Treatment and early Intervention in Psychosis Program Psychosis (TIPP) in Lausanne was measured using the following sets of criteria to define treatment onset; 1- initiation of antipsychotic medication, 2- entry into a specialised program and 3- entry into a specialised program and adequate medication with a good compliance.

Results: DUP varied greatly according to definitions, the most restrictive criteria leading to the longest DUP (Median DUP1=2.2, DUP2=7.4, DUP3=13.6 months). 19.7% of the patients who did not meet these restrictive criteria had poorer pre-morbid functioning and were more likely to use cannabis. Longer DUP3 was associated with poorer pre-morbid functioning and with younger age at onset of psychosis.

Conclusions: These results underline the need for a unique and standardised definition of the end of DUP. We suggest that the most restrictive definition of treatment should be employed when using the DUP concept in future research.

Introduction

Duration of untreated psychosis (DUP) broadly refers to the time elapsing between psychosis onset and treatment initiation, with its reduction being one of the main targets of early intervention strategies.[1] Despite a systematic review showing a significant, negative association between DUP and outcome,[2] results of such research are still a matter of controversy; some studies have shown a negative impact of long DUP on outcome,[3-6] while others have not.[7-10] These contradicting results may be linked to the wide variety of definitions of DUP.

The assessment of psychosis onset has been the object of considerable attention, resulting in a certain degree of consensus regarding its definition and the development of scales specifically designed to determine the date of its occurrence.[11] [12] However, this is not true for criteria applied to define the end of the DUP (E-DUP) period. Despite the availability of clear guidelines for the treatment of early psychosis,[13-15] the definition of treatment has varied greatly between studies. Definitions include: “initiation of medication”,[7 9 16-20] “start of any form of treatment”,[21] “initiation of adequate treatment”,[22] “time of first effective treatment”,[23] “hospitalization”[24 25] and “entry to a specialized program”.[26] Most of these definitions are likely to underestimate DUP;[27] entry to a program or prescription of medication does not mean that patients are sufficiently engaged to actually receive either satisfactory psychosocial support or adequate exposure to medication. Consequently, for many studies, DUP may be considered over when patients were actually far from receiving adequate treatment.[10 13] As a result, there is little generalisability across studies and investigations on DUP’s predictive validity may be of limited value.

In this study, we examined the clinical utility of various DUP definitions in first-episode psychosis (FEP) patients admitted in a specialised early intervention program. Three sets of criteria to define the E-DUP were studied. The first definition (E-DUP1) is based on the criterion most commonly used in the determination of DUP, which is initiation of the first antipsychotic treatment[7 9 16-20] regardless of its dosage and patients' adherence. The criterion defining E-DUP2, i.e. entering a specialised FEP program, is based on data suggesting that FEP patients receiving treatment in specialised programs have a better outcome[28 29] and lower disengagement rates[29-31] compared to patients treated in standard mental health facilities. E-DUP3 is the most restrictive, with patients being included in the specialised program, treated with antipsychotics and compliant to this treatment. This definition is in line with international guidelines to define adequate treatment for FEP patients, i.e. patients should be exposed to adapted psychosocial and pharmacological treatment.[13-15]

The aims of the study were: (1) To explore differences in DUP deriving from the three definitions of E-DUP; (2) To assess the prevalence of patients who do not reach restrictive criteria (E-DUP3); (3) To identify predictors of persistent failure to meet E-DUP3 criteria, as well as predictors of prolonged DUP according to E-DUP3 definition.

Methods

Participants and Setting

Since April 2004 a specialised program for early intervention in psychotic disorders, the Treatment and early Intervention in Psychosis Program (TIPP[32 33]), has been implemented in the Department of Psychiatry of the Lausanne University Hospital in Switzerland. Inclusion criteria are: age between 18 and 35, reside in the catchment

area (Lausanne and surroundings; population: about 250 000) and have met threshold criteria for psychosis, as defined by the “Psychosis threshold” subscale of the Comprehensive Assessment of At Risk Mental States scale (CAARMS[12]). Exclusion criteria are: more than a total of 6 months of anti-psychotic medication, psychosis related to intoxication or organic brain disease, IQ below 70.

The program is aimed at facilitating FEP patients’ access and engagement in treatment.[30 34] It comprises an outpatient clinic with case management, a specialised inpatient unit and a community treatment team.[35-37] Treatment is conducted on the basis of the International Early Psychosis Clinical Guidelines.[14] Patients are seen by case managers at least twice a week after discharge from any hospital admission, and once a week in the early phase of treatment (first 12 weeks). Retention of patients has been very high, with a rate of about 85%.[30] Approval has been granted by local ethics committee to access the TIPP database for research purposes. All patients who had been enrolled in the program for at least 18 months by March 2009 were considered for the present study.

Assessments

A specially designed questionnaire is routinely filled on the basis of information gathered from patients and their family after entry into TIPP. The questionnaire addresses demography, symptoms and functioning. Patients are also assessed prospectively (at months 2, 6, 12, 18, 24 and 36 by psychologist and case managers) in order to monitor symptomatic and functional evolution, as well as adherence to treatment and evolution of co-morbidities.

Premorbid characteristics: Premorbid functioning was assessed with the Global Assessment of Functioning Scale (GAF[38]), social and vocational functioning with the

Social and Occupational Functioning Assessment Scale (SOFAS[38]), and social adjustment with the Premorbid Adjustment Scale (PAS[39]). Familial socio-economical status was assessed according to parents' profession, as proposed by Chandola[40] and classified as: 1- high, 2- intermediate and 3- low. Migration was defined as being born outside of Switzerland. The severity of illness prior to admission to the clinical program was assessed using the Clinical Global Impressions-Severity of Illness scale (CGI-S[41]).

Characteristics at entry in the program: Level of functioning was assessed with the GAF and social and vocational functioning with the SOFAS. Substance use disorders (SUD) was evaluated according to the DSM-IV-TR[42] and with the Case Manager Rating Scale (CMRS[43]). Patients were also assessed regarding their insight into illness on a three point scale: 0- no insight (denying any behavioural change and any need for treatment); 1- partial insight (admits behavioural change but denies illness or need for treatment); 2- good insight (admits illness and agrees with need for treatment).

Outcome and clinical characteristics: Adherence to medication was assessed by case managers at each follow-up time line, based on interviews with patient and family. Ratings were defined as follows according to Keck and collaborators[44]: 1- Full adherence (taking medication as prescribed at least 75% of the time); 2- partial adherence (from 25% to 75% of the time); 3- non-adherence to medication (less than 25% compliance). Clinical diagnosis was based on DSM-IV criteria, using the Mini-International Neuropsychiatric Interview (M.I.N.I.[45]). Among co-morbid diagnoses, SUD, and more specifically Tetra-Hydro-Cannabinol (THC) use, were recorded separately from other co-morbidities, in order to allow separate analyses.

Measurement and definitions of DUP

Psychosis onset was defined using the Nottingham Onset Schedule[11] and the CAARMS exit criteria. TIPP's clinicians are trained to determine the date of onset of sustained positive psychotic symptoms on the basis of interview with patients and relatives. Where appropriate, this date can be modified over the course of treatment if new information allowing a more precise identification of this date is gathered, as patients become clinically more stable and more capable to reflect on symptom onset. A final decision regarding DUP was made on the basis of all available prospective data contained in the clinical file 18 months after entry in the program. To minimize the chance of diagnostic instability known to occur in patients presenting a first episode of psychosis[46], another evaluation of the diagnosis was done for patients who reached the 36-month benchmark.

E-DUP has been delineated on the basis of three situations frequently encountered in clinical and research settings: E-DUP1 was defined as the time of initiation of antipsychotic treatment, regardless of dosage and compliance; E-DUP2 was defined as the date of entry into TIPP; E-DUP3 was defined as being included in the TIPP, receiving adequate medication according to international guidelines[13-15] and taking medication at least 75% of the time for 4 weeks.[44] Three DUP values were obtained for each patient by calculating the time elapsed between psychosis onset and the dates when the various E-DUP criteria were met.

Data analyses

Skewness and kurtosis statistics were used to determine whether the data conformed to a normal Gaussian distribution[47]. Data normally distributed were presented descriptively in the form of means (M) and standard deviations *(*SD*)*. Otherwise,

descriptive statistics included the median ± 1st and 3rd quartiles. DUP values were not normally distributed and the effect of definition was assessed using the Friedman's Two Way ANOVA by Ranks. This was followed by multiple pairwise comparisons using the Wilcoxon's signed rank test with Bonferroni correction applied to alpha ($\alpha/3=0.05/3 =0.02$).

Two groups were derived based on whether the patient met the restrictive criteria (E-DUP3) or not. To determine differences between these two groups on premorbid, demographic, clinical and functional variables, the Mann-Witney test was used when the dependent variable was continuous and the chi-squared test (χ^2) when the dependent variables was categorical. For significant χ^2 ($p< 0.05$), there was examination of standardized residuals (z) to determine which cells contributed to the different chi-square value[48], only the p-values associated with the z-statistic are reported in the text.

Spearman's rho (r_s) correlation coefficient was used to examine the relationships between premorbid variables and length of DUP.

Analyses were performed using the Statistical Package for Social Sciences Version 15 (SPSS 15.0; Chicago, IL.).

Results

Patients' characteristics

A total of 156 patients had been in treatment for at least 18 months as of March 2009. Of these, three did not meet study criteria (diagnosis other then psychosis) and data was incomplete for 36 subjects. A total of 117 patients were included in the study.

Table 1 shows patient's demographic, premorbid and pre-admission to the TIPP attributes. Patients were predominantly males, displayed high socio-economic status and half of them had a history of migration. PAS score suggests that patients displayed a low premorbid level of functioning compared to the general population where a score lower than 0.2 is typically found.[39] At the time of their life when the severity of symptoms was at its worst, patients presented a high severity of illness reflected by a high CGI score, and low GAF and SOFAS scores.

Table 2 shows clinical and functional profiles at entry in the program. In line with other FEP cohorts,[49] many patients displayed a lack of insight. The majority of patients were suffering from schizophrenia and almost half of patients presented a SUD, typically cannabis. Some patients were diagnosed with one or more non-SUD co-morbidities: major depressive episode without psychotic symptoms (16.2%), personality disorder (9.4%), PTSD (4.3%), eating disorder (2.6%), dissociative disorder (1.7%), OCD (1.7%), anxiety disorder (0.85%) and social phobia (0.85%).

Duration of Untreated Psychosis

Figure 1 displays DUP values according to the three E-DUP definitions; differences between median DUP1, DUP2 and DUP3 were statistically significant (Friedman's χ^2 (2, n=94)=113.04, p<0.001). Median DUP1 (2.2 months) was significantly lower than DUP2 (7.4 months), and DUP3 (13.6 months) was significantly the longest among all three DUPs (DUP1-DUP2 (z=-5.608, p<0.002); DUP1-DUP3 (z=-7.904, p<0.020); DUP2-DUP3 (z=-5.409, p<0.020)).

Only 19.7% of the patients failed to fulfil the most restrictive definition of treatment (E-DUP3). Patients who did not meet DUP3 criteria had worse lifetime-SOFAS (p=0.017) and were more likely to use THC at entry in the program (χ^2 (1,

n=49)=4.241, p=0.039) when compared to those who did meet DUP3 criteria. No difference on demographic, and other pre-morbid or baseline characteristics were found.

Longer DUP3 was associated with younger age at psychosis onset (r_s =-0.573, p<0.001), higher PAS scores (r_s =0.373, p=0.001), lower best-lifetime GAF scores (r_s =-0.367, p<0.001) and lower best-lifetime SOFAS scores (r_s =-0.314, p=0.003).

Discussion

DUP is a widely used concept and its reduction is the focus of many early intervention programs. However, despite its importance, there is wide variability in how treatment onset is defined. The lack of consensus regarding E-DUP's definition limits its value in both clinical and research settings. This study compares three commonly used definitional models of DUP and shows how different the measured duration is from a definition to another. These results clearly show the importance of defining a unique and standardised definition of the end of DUP.

As expected, DUP varied strongly depending on how restrictively treatment initiation was defined. Consequently, failure to standardise the definition of DUP when exploring its impact on treatment characteristics and outcome in FEP, is likely to have contributed to a lack of generalisability across studies and inconsistencies in research findings. Unfortunately, review papers and meta-analysis in this domain have failed to take this element into account, and have therefore neglected a potentially significant confounding factor. As a consequence, in order to really clarify the issue of the potential impact of DUP on outcome in FEP, it is timely to propose a consensual definition for the end of the DUP period.

E-DUP1, defined by the initiation of the first antipsychotic treatment regardless of its dosage and patients' adherence was relatively brief in our sample (median of 2.2 months), reflecting a rapid diagnosis and access to pharmacological treatment. Indeed, due to global high standard of living and universal health insurance system, access to primary medical care is easy in the Lausanne region. However, reaching E-DUP1 criterion does neither mean that patients will be engaged in a therapeutic process, nor that they will continue to be compliant with the prescribed medication. In a previous study conducted in Lausanne before the implementation of a specialised early psychosis program[50], following a first hospitalisation, 48% of patients suffering from a FEP did not attend their first appointment in the outpatient clinic. Another recent study showed that FEP patients prescribed with antipsychotics are not necessarily compliant[33]. These observation underline the fact that a first contact with psychiatric services and the prescription of a pharmacological treatment is no guarantee for appropriate health services engagement and exposure to adequate treatment.

Patients with FEP who are treated in specialised first episode program have better outcomes[28 29] and lower rates of disengagement[29-31] compared to FEP patients treated in standard mental health facilities. Criterion defining E-DUP2, i.e. entering a specialised FEP program, is therefore relevant. The observation that DUP2 was more than 3 times longer than DUP1 is therefore concerning (median DUP2 = 7.37 months) and suggests that access to our program needs to be improved. This improvement could be achieved through awareness campaigns and strengthening of connections with primary care facilities.

De Haan[51] has suggested that delay in intensive psychosocial treatment may be a more important predictor of negative symptoms at outcome than is delay in introduction of antipsychotic alone. Similarly, current clinical guidelines for FEP treatment suggest that patients should be exposed to adapted psychosocial and pharmacological treatment.[10 13] In the present study, E-DUP3 definition criteria, which correspond to both engagement into a specialised program and FEP clinical guidelines regarding medication,[13-15] were reached only after a median of 13.63 months. DUP3 was almost six times longer than the time elapsing between psychosis onset and first prescription of antipsychotic medication (DUP1). This illustrates once again that early intervention in psychotic disorders goes beyond earlier diagnosis and medication prescription. Early intervention needs to include psycho-education and promotion of engagement of the patients.

The proportion of patients who failed to reach E-DUP3 criteria was 19.7%. This rate is in keeping with data stemming from a retrospective file audit study[49] conducted at the Early Psychosis Prevention and Intervention Centre (EPPIC, Melbourne, Australia), where 18.8% of patients were persistent medication refusers, defined as never taking antipsychotic for more than 3 consecutive weeks, over an 18-month treatment period.[33] Non-adherence to treatment and medication is a challenging issue for early intervention programs given that it is related to poorer outcome.[33]

Patient's characteristics that predicted failure to meet E-DUP3 criteria over the treatment period were examined. Early identification of these predictors may allow the implementation of specific strategies to promote treatment adherence. In line with previous findings,[33 52] a lower premorbid SOFAS was associated with failure to meet E-DUP3 criteria over the treatment period. Furthermore, cannabis use at entry to the

TIPP was also associated with the same outcome, underlying the importance of tailored intervention aimed at reducing substance abuse in FEP. Interestingly, poor insight and high CGI scores at entry were not correlated to later failure to meet E-DUP3 criteria, suggesting that severe clinical manifestations and absence of insight at baseline should not lead to undue pessimism regarding capacity of patients to later engage in treatment.

The present study also aimed at identifying which characteristics were associated with a longer DUP when treatment was defined by restrictive criteria (E-DUP3). In line with other studies,[6 53 54] younger age at onset of psychosis and poorer premorbid level of functioning (higher PAS score, low scores of best-lifetime SOFAS and GAF) were associated with longer DUP3. However, contrary to findings from Peralta[55], no correlation between lower socio-economic status and DUP3 was found. This may be due to differences between samples and the small number of patients with low socio-economic status in the sample used in the present study.

A few limitations should be considered when interpreting these results. First, even if a consensus exists regarding the definition and the tools that can be applied to define psychosis onset[11 12], a precise dating of this event remains subject to a potentially great amount of imprecision. However, a particular effort was made to update relevant data throughout the treatment period whenever new information allowed a more precise estimation of this date. Secondly, the sample size was rather small, and results may not be generalised to FEP patients treated in other socio-economic context. However, despite these limitations, the fact that all consecutive patients treated in the program were entered in the study provides a sample that is likely to be highly representative of FEP patients treated in the Lausanne area.

In conclusion, the present results clearly show that the absence of a consensus for the definition of the end of DUP can lead to major differences in the determination of time elapsing between psychosis onset and treatment initiation. Thus, there is an urgent need to harmonise criteria applied in studies exploring the impact of DUP on outcome in FEP. DUP has been put forward as a key target for early intervention. However, the controversy about its validity as an outcome predictor has become on focus of criticism for those who question the relevance of early intervention strategies. If one is to assess the impact of DUP in psychotic disorders, definition of treatment needs to correspond to what expert consensus have defined as adequate treatment of a FEP. This is likely to shed light on the unfortunately high proportion of patients who do not receive adequate treatment despite the implementation of specialised programs. In turn, in addition to allow a better evaluation of the impact of treatment delay in psychotic disorders, it could inspire both clinicians and researchers to develop new strategies to help patients to adhere to treatment. Therefore, we propose to use the restrictive definition of the end of DUP that corresponds to these criteria in any clinical or research setting interested in using this measurement.

Tables and figure

Table 1: Demographic and premorbid attributes

Variables of interest	Value	n
Patients		117
Age at entry (Years: Mean ± SD)	24.7 ± 4.2	117
Gender Male (%)	65.8	77
Socio-Economic Status (%)	100	107
High	57.9	62
Intermediate	31.8	34
Low	10.3	11
Migration (%)	49.6	58
Age at onset of psychosis (Mean ± SD)	22.9 ± 5.0	117
PAS (Mean ± SD)	0.37 ± 0.16	99
Worst lifetime CGI (Mean ± SD)	6.1 ± 0.8	83
Worst lifetime GAF (Mean ± SD)	24.3 ± 11.6	95
Worst lifetime SOFAS (Mean ± SD)	28.0 ± 13.1	95
Best lifetime GAF (Mean ± SD)	74.1 ± 12.2	109
Best lifetime SOFAS (Mean ± SD)	74.9 ± 12.6	107

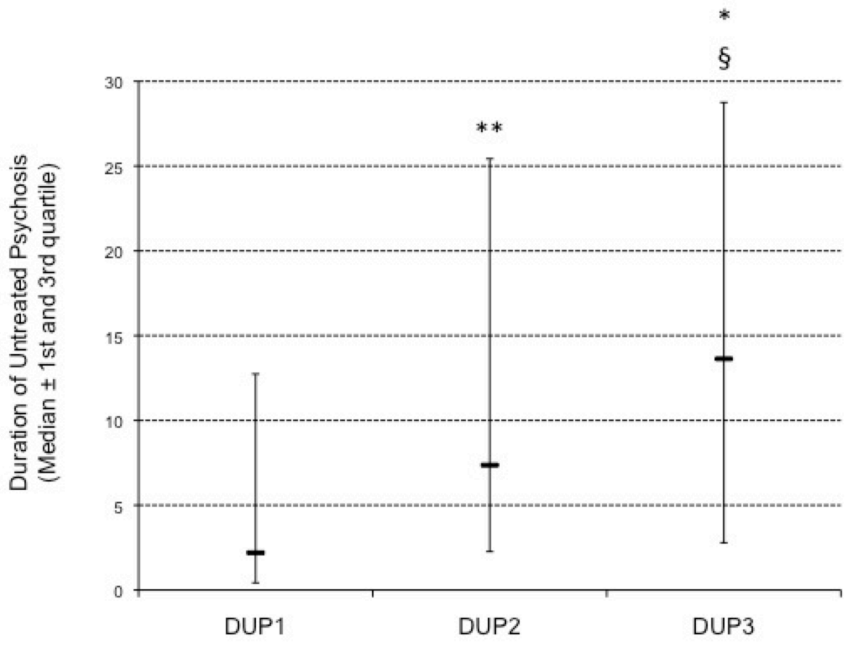
PAS: Premorbid Adjustment Scale; CGI: Clinical Global Impressions-severity of illness scale; GAF: Global Assessment of Functioning scale ; SOFAS: Social and Occupational Functioning Assessment Scale

Table 2: Clinical and functional profile of patients at entry in the Program

Variables of interest	Value	n
Patients		117
Insight at Entry (%)	100	105
Poor	42.9	45
Partial	43.8	46
Good	14.3	15
GAF at Entry (Mean ± SD)	31.8 ± 14.1	105
SOFAS at Entry (Mean ± SD)	34.4 ± 13.7	101
Diagnosis (%)	100	117
Schizophrenia	69.2	81
Schizophreniform psychosis	8.5	10
Schizoaffective disorder	7.7	9
Bipolar disorder	6.8	8
Major depression with psychotic features	2.6	3
Other	5.1	6
Comorbidity Axis I (Without SUD)	37.6	43
Comorbidity Axis II	17.1	20
Dependance	47	55
THC dependance	41.9	49

GAF: Global Assessment of Functioning scale ; SOFAS: Social and Occupational Functioning Assessment Scale; SUD: Substance Use Disorder; THC: TetraHydro Cannabinol

Figure 1: Duration of Untreated Psychosis values following the application of three definitions of treatment



* Significant difference compared to DUP1, § Significant difference compared to DUP 2
* or § p<0.05, ** p<0.01

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